Original Article

The combination of maximum standardized uptake value and clinical parameters for improving the accuracy in distinguishing primary mediastinal lymphomas from thymic epithelial tumors

Hui Yan[1,2#], Lihua Wang[2#], Bei Lei[2], Maomei Ruan[2], Cheng Chang[2], Mingge Zhou[1], Liu Liu[2], Wenhui Xie[2], Yuetao Wang[1]

[1]Department of Nuclear Medicine, The Third Affiliated Hospital of Soochow University, Changzhou, China; [2]Department of Nuclear Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Contributions: (I) Conception and design: H Yan, L Liu, W Xie, Y Wang; (II) Administrative support: W Xie, Y Wang; (III) Provision of study materials or patients: C Chang; (IV) Collection and assembly of data: L Wang, B Lei; (V) Data analysis and interpretation: M Ruan, M Zhou; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Yuetao Wang, MD, PhD. Department of Nuclear Medicine, The Third Affiliated Hospital of Soochow University, No. 185, Juqian Street, Tianning District, Changzhou 213003, China. Email: yuetao-w@163.com; Wenhui Xie, MD, PhD; Liu Liu, MD, PhD. Department of Nuclear Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, No. 241, Huaihai West Road, Xuhui District, Shanghai 200030, China. Email: shxknuclear@126.com; chestnuclear@126.com.

Background: Anterior mediastinal masses are relatively uncommon, and mediastinal lymphomas are the malignancies most likely to be confused with thymic epithelial tumors (TETs). The aim of this study was to investigate whether the combination of ^{18}fluorine-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) findings and clinical parameters is useful in differentiating lymphoma from TETs in anterior mediastinal masses.

Methods: This retrospective study consecutively included 304 patients with anterior mediastinal masses (244 TETs and 60 lymphomas) who underwent ^{18}F-FDG PET-CT 1 to 2 weeks before tumor resection or biopsy between August 2016 and March 2022. The correlations between the maximum standardized uptake value (SUVmax) of tumors and clinical parameters of patients with histology subtypes were analyzed. Receiver operating characteristic curve analysis was used to obtain the optimal cutoff values of age, lactate dehydrogenase (LDH), tumor size, and SUVmax to predict lymphoma. Logistic regression analysis was used to identify potential predictive factors for lymphoma.

Results: Lymphoma was significantly associated with younger patient age, higher LDH level, larger tumor size, and higher SUVmax compared to TETs (P<0.001). In the modeling cohort, age ≤40.5 years, LDH level ≥197 U/L, tumor size ≥10.72 cm, and SUVmax ≥11.95 were identified as independent predictors for lymphoma with odds ratios of 20.14 [95% confidence interval (CI): 6.02–67.40; P<0.001], 4.89 (95% CI: 1.27–18.89; P=0.021), 8.82 (95% CI: 2.31–33.69; P=0.001), and 30.01 (95% CI: 6.59–136.72; P<0.001), respectively. The accuracy of age, LDH, tumor size, and SUVmax in predicting lymphoma was 84.8%, 67.8%, 85.2%, and 78.3% respectively. The combination of the four above parameters could improve the predictive accuracy to 89.1%, and in the validation cohort, this combination increased the predictive accuracy to 87.8%.

Conclusions: SUVmax on ^{18}F-FDG PET-CT has the potential ability to discriminate lymphomas from TETs in the diagnosis of anterior mediastinal masses, and the combination of SUVmax with clinical parameters can improve the diagnostic accuracy. This combination may therefore may be helpful in avoiding unnecessary operation in patients with anterior mediastinal lymphomas.

Keywords: Positron emission tomography-computed tomography (PET-CT); anterior mediastinal masses; lymphoma; thymic epithelial tumors (TETs)

Submitted Apr 12, 2023. Accepted for publication Nov 24, 2023. Published online Jan 05, 2024.
doi: 10.21037/qims-23-496
View this article at: https://dx.doi.org/10.21037/qims-23-496

Introduction

Mediastinal tumors are relatively uncommon, and more than half (about 59%) of masses in the anterior compartment are pathologically diagnosed as malignant tumors (1). The pathological types of primary anterior mediastinal masses include cyst, thymic hyperplasia, thymoma, thymic carcinoma, thymic neuroendocrine neoplasm, germ cell tumor, and lymphoma, among which thymic epithelial tumors (TETs; including thymoma, thymic carcinoma, and thymic neuroendocrine neoplasm) and lymphoma are the two most common types (2). The treatment strategies of TETs and lymphomas are almost completely different: surgery is suggested for most TETs, whereas immunochemotherapy and/or radiotherapy is more appropriate for the treatment of lymphomas (3,4). Traditional imaging modalities [e.g., computed tomography (CT) and magnetic resonance imaging (MRI)] have been widely used in clinical practice to evaluate mediastinal tumors; however, the similarity of TETs and lymphomas in morphologic assessment performed by traditional imaging technics consistently leads to misdiagnosis, thereby resulting in ineffective or inaccurate management and therapy (e.g., Ackman *et al.* reported a high rate of 59.4% of lymphomas with nontherapeutic thymectomy) (5). Therefore, the discrimination of lymphomas with TETs before treatment is essential for developing appropriately varied treatment strategies for anterior mediastinal masses.

Invasive biopsy is the only means to histologically diagnosing isolated anterior mediastinal masses; unfortunately, some patients are unable to obtain a pathological diagnosis due to certain reasons, such as an aversion to undergoing invasive examination, a physical debilitation preventing mediastinal lesion biopsy, or an insufficient sample volume in mediastinal lesion biopsy. However, as the most widely used molecular imaging modality for tumor diagnosis, ^{18}fluorine-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) can provide information on glucose metabolism from different tumors and enable the noninvasive diagnosis of tumors. The maximum standardized uptake value (SUVmax) is the most commonly used ^{18}F-FDG PET-CT parameter for tumor diagnosis and is able to reflect the glycolytic activity of tumors (6). Recently, the SUVmax of lymphomas was found to be significantly higher than that of TETs [except in several non-PET-avid subtypes such as mucosa-associated lymphoid tissue (MALT) lymphoma] (7,8); however, the accuracy, sensitivity, and specificity of SUVmax to predict anterior mediastinal lymphomas are all only about 70.0% and need to be improved (9). Since certain clinical parameters [e.g., gender, age, lactate dehydrogenase (LDH) level] were also demonstrated to be potential biomarkers of lymphomas or TETs (10), we speculate that the combination of clinical parameters may improve the accuracy of SUVmax for diagnosing anterior mediastinal lymphomas.

To investigate whether the combination of ^{18}F-FDG PET-CT findings and clinical parameters can help differentiate anterior mediastinal lymphomas from TETs, this study analyzed the correlation between ^{18}F-FDG SUVmax and clinical parameters [including gender, age, serum leukocytes, hemoglobin (Hb), LDH, and tumor size] and histology subtypes of TETs and lymphomas in anterior mediastinal masses. We present this article in accordance with the STARD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-496/rc).

Methods

Study population

There were a total of 476 patients with anterior mediastinal masses who underwent ^{18}F-FDG PET-CT 1 to 2 weeks before tumor resection or biopsy between August 2016 to March 2022 at Shanghai Chest Hospital. Ultimately, 304 patients histologically diagnosed with TETs and lymphomas were enrolled in this retrospective study (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Review Board of Shanghai Chest Hospital (No. KS1753). Individual consent for this retrospective analysis was waived.

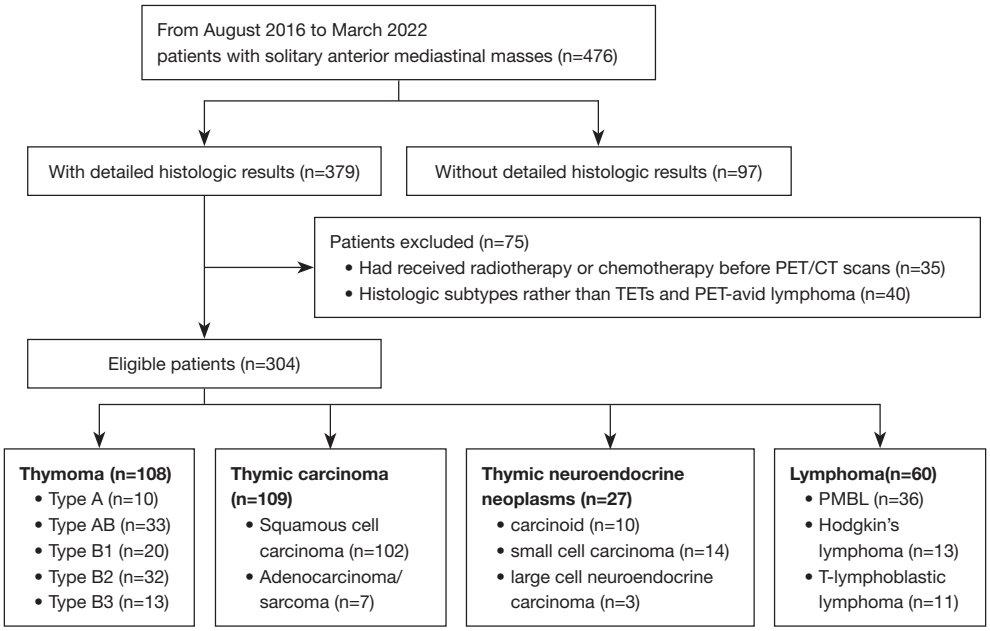

Figure 1 Study flowchart shows inclusion and exclusion criteria. A total of 304 patients with anterior mediastinal masses underwent ^{18}F-FDG PET-CT 1 to 2 weeks before tumor resection or biopsy between August 2016 to March 2022. ^{18}F-FDG PET-CT, ^{18}fluorine-fluorodeoxyglucose positron emission tomography-computed tomography; TETs, thymic epithelial tumors; PMBL, primary mediastinal large B-cell lymphoma.

The inclusion criteria for patients were as follows: (I) presence of anterior mediastinal mass, (II) confirmation via histologic examination, (III) no history of any mediastinal mass-associated treatment before PET-CT, and (IV) availability of pathologic findings. Meanwhile, the exclusion criteria were as follows: (I) no detailed histologic results (n=97), (II) a history of radiotherapy or chemotherapy before PET-CT (n=35), (III) a histologic subtype other than TETs and PET-avid lymphomas [germ cell tumor (n=18), MALT lymphoma (n=3), thymic benign tumor (n=11), and other rare tumors (n=8)]. Records of included patients were reviewed to retrieve information on gender, age, serum leukocytes, Hb, and LDH levels (normal value 120–250 U/L at our institution).

According to a stratified analysis, patients were randomly assigned in a 7:3 ratio to cohorts for the modeling (n=230) and validation (n=74) of lymphoma predictors.

PET-CT imaging

^{18}F-FDG PET-CT was performed after patients fasted for at least 6 hours and 60 min after an intravenous administration of ^{18}F-FDG (3.7 MBq per kilogram of body weight, radiochemical purity 95%) provided by Shanghai Kexin Pharmaceutical (Shanghai, China). The blood glucose levels were measured just prior to tracer administration, and a maximal blood glucose level of 140 mg/dL was required for optimal ^{18}F-FDG uptake.

Imaging was performed with a combined PET-CT device (Biograph mCT 64; Siemens Healthineers, Erlangen, Germany). CT scanning (120 keV, 30–100 mA in auto mA mode, 5.00-mm slice thickness) was first performed without contrast material administration. Immediately after CT scanning, PET imaging was performed with an acquisition time of 3 minutes per bed position. The regions of interest (ROIs) of primary lesions were manually defined, and SUVmax and diameters were independently recorded by two experienced nuclear medicine physicians (W.X. and C.C., with approximately 20 and 15 years of experience in the interpretation of PET-CT images, respectively) blinded to the study design. The differences between physicians' assessments were resolved by consensus through discussion, and they reached an almost perfect agreement.

Histologic classification

Based on the 2021 World Health Organization (WHO) classification system (11), thymomas were classified into the

five following subtypes depending on the morphology of epithelial cells and the lymphocyte-to-epithelial cell ratio: type A, AB, B1, B2, and B3. If a thymoma was composed of diverse (two or more) histologic subtypes (n=12), we selected the higher grade tumor subtype, irrespective of the extent of each subtype. According to previous reports (12,13), we classified thymoma into two groups: low-risk thymoma (type A, AB, and B1) and high-risk thymoma (type B2 and B3). Thymic carcinomas, which include thymic squamous cell carcinoma, adenocarcinoma, and sarcoma, exhibit a similar morphology to that of malignant neoplasms arising from other organs besides thymomas. Thymic neuroendocrine neoplasms include carcinoid tumor, small cell carcinoma, and large-cell neuroendocrine carcinoma. Regarding mediastinal lymphoma, we chose the three most common types: primary mediastinal large B-cell lymphoma, Hodgkin lymphoma, and T-lymphoblastic lymphoma (1).

Statistical analysis

Data were analyzed with SPSS software version 24.0 (IBM Corp., Armonk, NY, USA), GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA), and MedCalc version 20.211 (MedCalc Software Ltd., Ostend, Belgium). Quantitative data conforming to a normal distribution are presented as the mean ± standard deviation (SD) values. The unpaired two-tailed *t*-test or one-way analysis of variance (ANOVA) test was used to determine the association of age, gender, leukocytes, Hb, LDH, tumor size, and SUVmax between different histologic types in independent samples. The area under the receiver operating characteristic (ROC) curve (AUC) was calculated, and the DeLong test was used to compare AUCs and the cutoff values, with the highest Youden index being used as the optimal cutoff threshold for lymphoma diagnosis. Logistic regression analysis was used to assay the prediction rate of lymphoma among the three risk groups. A two-tailed P value <0.05 indicated a significant difference.

Results

Study population

A total of 304 patients (169 males and 135 females; age range, 12–79 years) who had anterior mediastinal masses and received ^{18}F-FDG PET-CT scans were included in this retrospective study. Histologic confirmation of mediastinal masses was obtained via surgery or biopsy. As listed in *Table 1*, 108 of 304 patients (35.5%) were found with thymoma (type A: n=10; type AB: n=33; type B1: n=20; type B2: n=32; type B3: n=13), 109 of 304 patients (35.9%) were found with thymic carcinoma (squamous cell carcinoma: n=102; adenocarcinoma/sarcoma: n=7), 27 of 304 patients (8.9%) were identified with thymic neuroendocrine neoplasms (carcinoid tumor: n=10; small-cell carcinoma: n=14; large-cell neuroendocrine carcinoma: n=3), and 60 of 304 patients (19.7%) were identified with lymphoma. Among 60 patients with lymphoma, more than half (36/60, 60.0%) had primary mediastinal large B-cell lymphoma, with other types of lymphoma including Hodgkin lymphoma (13/60, 21.7%) and T-lymphoblastic lymphoma (11/60, 18.3%).

The characteristics of patients in the modeling and validation cohorts are also listed in *Table 1*; there was no significant difference in patient characteristics (age, gender, and pathological type) between the modeling and validation cohorts (P=0.19–0.97). Moreover, 159 patients underwent surgery, and 145 patients underwent needle biopsy. The differences of ways to obtain pathology between modeling and validation cohorts were not statistically significant (P=0.21).

Age, serum LDH, tumor size, and SUVmax differed across the five groups in the modeling cohort

To investigate the correlation of clinical and ^{18}F-FDG metabolic features with different histological subtypes of anterior mediastinal masses, we analyzed the differences in gender, age, serum leukocytes, Hb, LDH, tumor size, and SUVmax of tumor in five anterior mediastinal mass groups (*Table 2*). This analysis indicated that the age of patients with lymphoma was significantly lower than that of those with low-risk thymoma, high-risk thymoma, thymic carcinoma, or thymic neuroendocrine neoplasms (P<0.001) (*Figure 2A*). Serum LDH level, tumor size, and SUVmax in those with lymphoma were all significantly higher than those in patients in the other four groups (all P values <0.001) (*Figure 2B-2D*), whereas gender, leukocytes, and Hb were not significantly different among the different types of anterior mediastinal masses (P=0.22–0.75).

Age, serum LDH, tumor size, and SUVmax were independent predictors of lymphoma

ROC analysis was next performed to obtain the optimal cutoff values of age, LDH, tumor size, and SUVmax to predict lymphoma in anterior mediastinal masses. In the

Table 1 Patient demographics by histological subtype of anterior mediastinal masses

Factors	All patients (n=304)	Modeling cohort (n=230)	Validation cohort (n=74)	P value
Age (years), median [interquartile range]	53 [12–79]	53 [12–79]	54 [19–75]	0.97
Gender				0.19
Male	169	123	46	
Female	135	107	28	
Histologic type				
Thymoma	108	82	26	0.79
A	10	7	3	
AB	33	24	9	
B1	20	17	3	
B2	32	25	7	
B3	13	9	4	
Thymic carcinoma	109	84	25	0.57
Squamous cell carcinoma	102	78	24	
Adenocarcinoma/sarcoma	7	6	1	
Thymic neuroendocrine neoplasm	27	20	7	0.38
Carcinoid	10	8	2	
Small-cell carcinoma	14	9	5	
Large-cell neuroendocrine carcinoma	3	3	0	
Lymphoma	60	44	16	0.68
PMBL	36	25	11	
Hodgkin lymphoma	13	10	3	
TLL	11	9	2	
Pathologic procedure				0.21
Surgery	159	125	34	
Needle biopsy	145	105	40	

PMBL, primary mediastinal large B-cell lymphoma; TLL, T-lymphoblastic lymphoma.

results (*Table 3*, *Figure 3*), the optimal cutoff values for age, LDH, tumor size, and SUVmax to predict lymphoma were 40.5 years (accuracy 84.8%), 197 U/L (accuracy 67.8%), 10.72 cm (accuracy 85.2%), and 11.95 (accuracy 78.3%), respectively (AUC =0.802–0.890).

Univariate and multivariate logistic regression analyses were subsequently performed to identify the potential predictive factors for lymphoma in anterior mediastinal masses (*Table 3*). In the univariate analysis, young age, high serum LDH, large tumor size, and high SUVmax were significantly associated with anterior mediastinal lymphoma (all P values <0.001). Subsequent multivariate logistic regression analysis further revealed that age, LDH, tumor size, and SUVmax were independent predictors for lymphoma (P<0.001 to P=0.021). Young age was strongly associated with lymphoma, with an odds ratio (OR) value of 20.14 [95% confidence interval (CI): 6.02–67.40; P<0.001]. High LDH, tumor size, and SUVmax values were associated with an increased risk for lymphoma, with an OR value of 4.89 (95% CI: 1.27–18.89; P=0.021), 8.82 (95% CI: 2.31–33.69; P=0.001), and 30.01 (95% CI: 6.59–136.72; P<0.001), respectively.

Table 2 Comparison of clinic features and SUVmax across different histological subtypes of anterior mediastinal masses in the modeling cohort

Factors	All patients (n=230)	Low-risk thymoma (n=48)	High-risk thymoma (n=34)	Thymic carcinoma (n=84)	Thymic neuroendocrine neoplasm (n=20)	Lymphoma (n=44)	P value
Gender (M/F)	123/107	23/25	14/20	49/35	14/6	23/21	0.22
Age (years)	50.40±15.64	52.73±13.04	50.09±14.79	56.58±12.07	59.85±9.37	32.00±12.72	<0.001
Leukocytes (10^9/L)	7.25±2.72	6.95±1.75	6.51±2.59	7.36±2.57	7.37±2.44	7.90±3.83	0.22
Hb (g/L)	137.03±17.99	137.48±20.58	140.12±15.32	137.08±16.79	135.80±18.80	134.58±19.15	0.75
LDH (U/L)	249.49±163.25	188.17±46.74	185.32±33.74	225.58±92.33	242.25±109.71	414.89±283.40	<0.001
Tumor size (cm)	7.83±3.00	6.83±2.57	7.50±1.91	6.79±2.60	8.97±2.64	10.63±3.14	<0.001
SUVmax	12.00±7.82	5.64±2.26	7.18±2.68	12.36±5.51	12.82±7.42	21.63±8.55	<0.001

Data are presented as n or mean ± standard deviation. SUVmax, maximum standardized uptake value; M, male; F, female; Hb, hemoglobin; LDH, lactate dehydrogenase.

To investigate that whether the combination of age, LDH, tumor size, and SUVmax could improve the predictive accuracy for lymphoma in anterior mediastinal masses, we next compared the probability of lymphomas being present in a high-risk group (age ≤40.5 years, LDH ≥197 U/L, tumor size ≥10.72 cm, and SUVmax ≥11.95), moderate-risk group (other than age ≤40.5 years, LDH ≥197 U/L, tumor size ≥10.72 cm, and SUVmax ≥11.95 or age >40.5 years, LDH <197 U/L, tumor size <10.72 cm, and SUVmax <11.95), and a low-risk group (age >40.5 years, LDH <197 U/L, tumor size <10.72 cm, and SUVmax <11.95) in the modeling cohort. The probability of lymphoma presence in the low-, moderate-, and high-risk groups were 0.0% (0/77), 18.2% (24/132), and 95.2% (20/21), respectively, while the probability TET presence in the low-, moderate-, and high-risk groups were 100.0% (77/77), 81.8% (108/132), and 4.8% (1/21), respectively (P<0.001; *Table 4*). We also calculated the accuracy of the high-risk group for predicting lymphoma and observed that the accuracy of the combined parameters to predict lymphoma was 89.1% (205/230). Furthermore, when age, LDH, tumor size, and SUVmax were combined in ROC analysis, the AUC (0.963; 95% CI: 0.935–0.991) was significantly higher than that of any of these parameters used alone (all P values <0.05) (*Figure 3*).

Age, LDH, tumor size, and SUVmax were proven to be independent predictors for anterior mediastinal lymphoma, and their combination could improve the predictive accuracy for lymphoma. Representative examples are shown in *Figure 4*.

Validation of the effectiveness of age, LDH, tumor size, and SUVmax to predict lymphoma

To validate the effectiveness of the above mentioned cutoff values to predict lymphoma, we next analyzed the probabilities of lymphoma presence in young and old age, low and high LDH level, small and large tumor size, and low and high SUVmax in the validation cohort and confirmed that the probability of lymphoma was 59.1% (13/22), 34.9% (15/43), 56.2% (9/16), and 53.6% (15/28), respectively. The accuracy of predicting lymphoma using age, LDH, tumor size, and SUVmax based on the abovementioned cutoff values was 83.8% (62/74), 60.8% (45/74), 81.1% (60/74), and 81.1% (60/74), respectively (all P values ≤0.05; *Table 5*).

To validate the effectiveness of the combination of age, LDH, tumor size, and SUVmax as a predictor of lymphoma in anterior mediastinal masses, we performed the same procedure as that described above in the validation cohort. The analysis revealed that the probabilities of lymphoma presence in the low-, moderate-, and high-risk groups were 0.0% (0/19), 18.8% (9/48), and 100.0% (7/7), respectively, while the probabilities of TET presence in the low-, moderate-, and high-risk groups were 100.0% (19/19), 81.2% (39/48), and 0.0% (0/7), respectively (P<0.001; *Table 4*). The accuracy of the high-risk group for predicting lymphoma was 87.8% (65/74). These data validated the superiority of the combined use of age, LDH, tumor size, and SUVmax for predicting lymphoma over the use of any these parameters used alone.

This study not only demonstrated the potential of age,

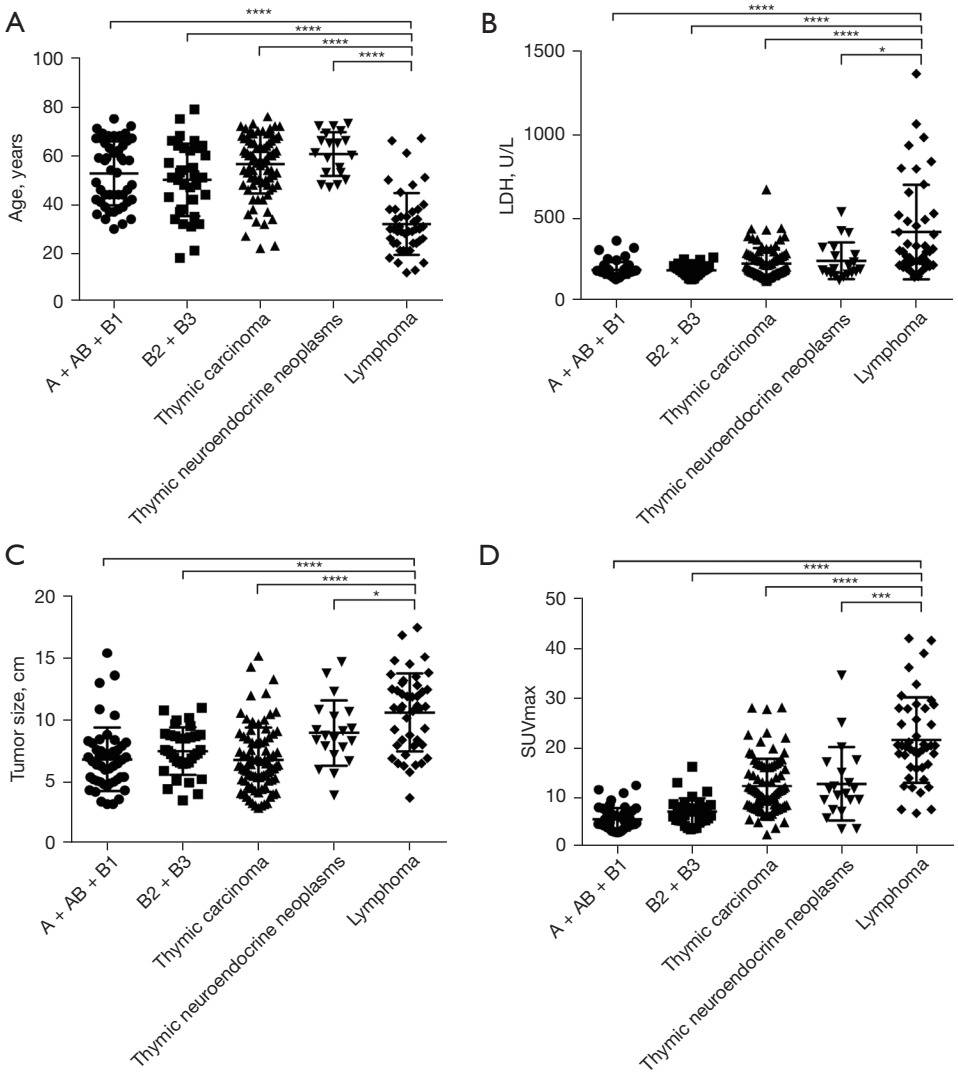

Figure 2 Correlation between clinical and ^{18}F-FDG metabolic features in different pathologic types of anterior mediastinal masses. (A-D) The distribution of age, LDH, tumor size, and SUVmax, respectively. *, P<0.05; ***, P<0.001; ****, P<0.0001. LDH, lactate dehydrogenase, SUVmax, maximum standardized uptake value; ^{18}F-FDG, ^{18}fluorine-fluorodeoxyglucose.

Table 3 Receiver operating characteristic curve analysis and univariate and multivariate logistic regression analyses of predictive factors for lymphoma in anterior mediastinal masses in the modeling cohort

Factors	Cutoff value	AUC (95% CI)	Accuracy	Univariate analysis		Multivariate analysis	
				OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	40.5	0.886 (0.826–0.947)	84.8%	29.83 (12.10–73.53)	<0.001	20.14 (6.02–67.40)	<0.001
LDH (U/L)	197	0.817 (0.748–0.886)	67.8%	16.57 (5.69–48.30)	<0.001	4.89 (1.27–18.89)	0.021
Tumor size (cm)	10.72	0.802 (0.727–0.876)	85.2%	16.47 (7.40–36.64)	<0.001	8.82 (2.31–33.69)	0.001
SUVmax	11.95	0.890 (0.838–0.942)	78.3%	30.44 (10.33–89.66)	<0.001	30.01 (6.59–136.72)	<0.001

AUC, area under the curve; CI, confidence interval; OR, odds ratio; LDH, lactate dehydrogenase; SUVmax, maximum standardized uptake value.

LDH, tumor size, and SUVmax used alone to predict lymphoma in anterior mediastinal masses but also proved the superiority of their combination for prediction in this scenario.

Discussion

This study's principal aim was to investigate whether the combination of SUVmax with clinical parameters could improve diagnostic accuracy in differentiating lymphoma and TETs in anterior mediastinal masses. The major findings were as follows: First, younger patient age, higher LDH level, larger tumor size, and higher SUVmax were associated with lymphoma in patients with anterior mediastinum masses. Second, age (≤40.5 years), LDH (≥197 U/L), tumor size (≥10.72 cm), and SUVmax (≥11.95) were each independent predictors for lymphoma. Third, the combination of age, LDH, tumor size, and SUVmax could increase the accuracy of each parameter alone to predict lymphoma, with a high predictive accuracy in the modeling (from 67.8–84.8% to 89.1%) and validation (from 81.1–83.8% to 87.8%) cohorts and a significantly high AUC in the ROC analysis (0.802–0.890 *vs.* 0.963). Indeed, previous studies have reported that lymphoma tends to occur in young adults, LDH is elevated in lymphomas (14), and the mean maximal diameter and SUVmax of lymphomas are significantly higher than those of TETs (15,16), which is consistent with our results. However, to our knowledge, our study is the first to combine SUVmax with clinical parameters and includes the largest sample used to investigate the differentiation of primary mediastinal lymphomas from TETs in anterior mediastinal masses.

Primary mediastinal lymphoma usually occurs in the anterior mediastinum, and lymphoma accounts for nearly 20% of all mediastinum neoplasms in adults and 50% in children (17). The discrimination of lymphoma and TETs is difficult due their associated low CT and MRI diagnostic efficiency and a lack of specific tumor markers (18,19). As the most well-known of the metabolic functional imaging techniques, ^{18}F-FDG PET-CT can provide the metabolic

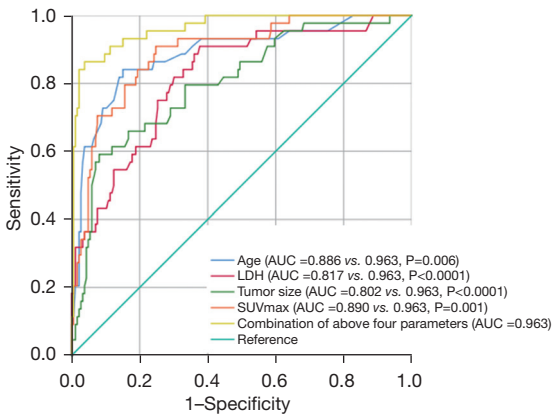

Figure 3 AUC for age, LDH, tumor size, SUVmax, and their combination in predicting lymphoma in the modeling cohort. The optimal cutoff values for age, LDH, tumor size, and SUVmax were 40.5 years (AUC =0.886; 95% CI: 0.826–0.947), 197 U/L (AUC =0.817; 95% CI: 0.748–0.886), 10.72 cm (AUC =0.802; 95% CI: 0.727–0.876), and 11.95 (AUC =0.890; 95% CI: 0.838–0.942), respectively. The combination of parameters yielded an AUC of 0.963 (95% CI: 0.935–0.991). AUC, area under the receiver operating characteristic curve; LDH, lactate dehydrogenase, SUVmax, maximum standardized uptake value.

Table 4 Prediction of lymphoma in the low-, moderate-, and high-risk groups in modeling and validation cohort

Group	All patients, N	Probability of TET, % (n/N)	Probability of lymphoma, % (n/N)	P value
Modeling cohort				<0.001
Low risk	77	100.0 (77/77)	0.0 (0/77)	
Moderate risk	132	81.8 (108/132)	18.2 (24/132)	
High risk	21	4.8 (1/21)	95.2 (20/21)	
Validation cohort				<0.001
Low risk	19	100.0 (19/19)	0.0 (0/19)	
Moderate risk	48	81.2 (39/48)	18.8 (9/48)	
High risk	7	0.0 (0/7)	100.0 (7/7)	

TET, thymic epithelial tumor.

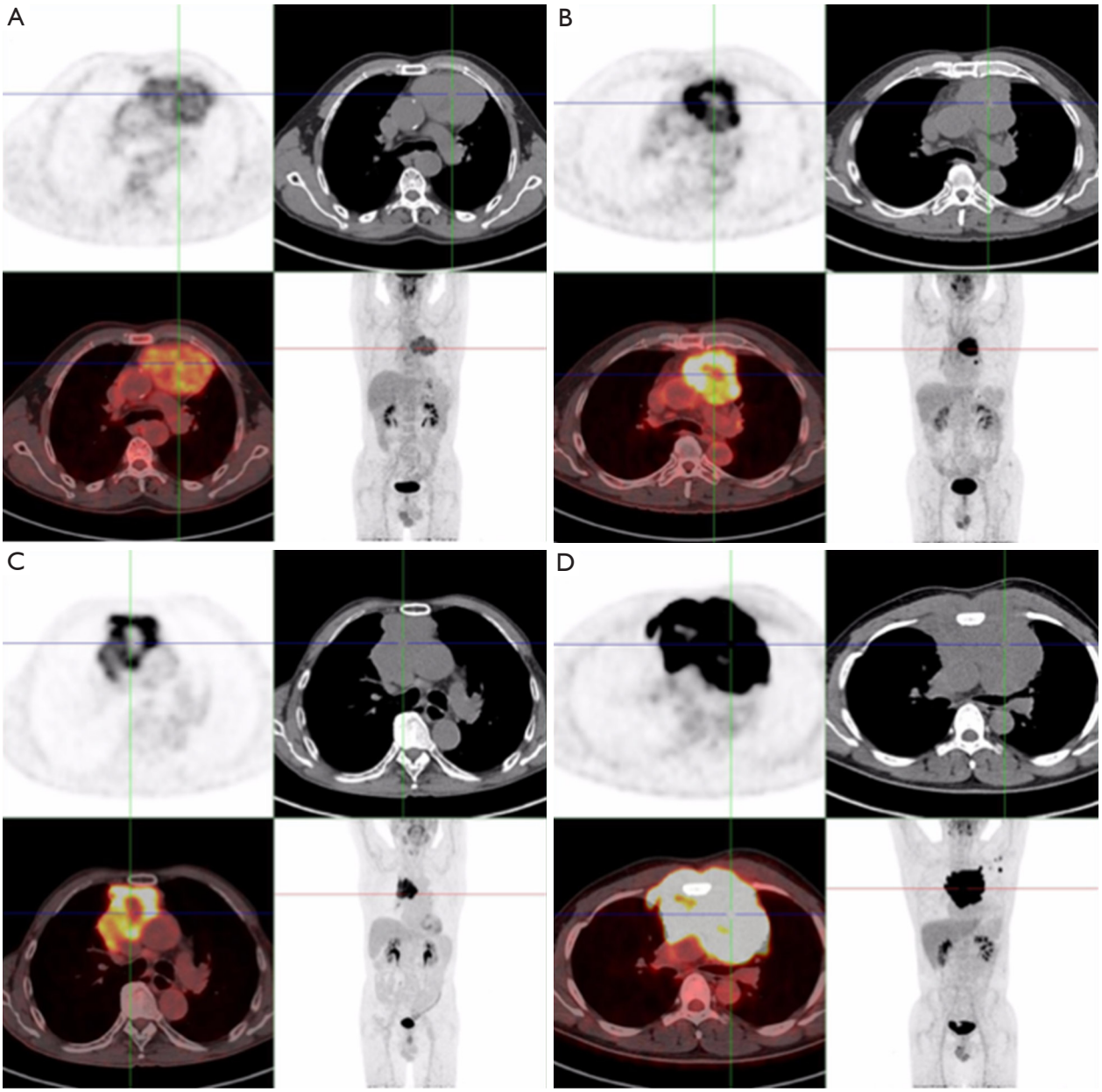

Figure 4 ^{18}F-FDG PET-CT images of different pathologic types of anterior mediastinal masses. (A) Images in a 67-year-old man 5 days before tumor resection, with a LDH level of 183 U/L, a tumor size of 8.3 cm, and a lesion with an ^{18}F-FDG uptake (SUVmax) of 5.6. The pathologic analysis revealed type A thymoma. (B) Images in a 70-year-old man 1 week before tumor biopsy, with an LDH level of 139 U/L, a tumor size of 7.1 cm, and an SUVmax of 8.0. The pathologic analysis revealed thymic squamous cell carcinoma. (C) Images in a 69-year-old man 10 days before tumor resection, with an LDH level of 178 U/L, a tumor size of 7.8 cm, and an SUVmax of 10.4. The pathologic analysis revealed small cell carcinoma. (D) Images in a 35-year-old man 10 days before tumor biopsy, with an LDH level of 480 U/L, a tumor size of 12.2 cm, and an SUVmax of 36.0. The pathologic analysis revealed primary mediastinal large B-cell lymphoma. ^{18}F-FDG PET-CT, 18fluorine-fluorodeoxyglucose positron emission tomography-computed tomography; LDH, lactate dehydrogenase, SUVmax, maximum standardized uptake value.

Table 5 Prediction of lymphoma in the low- and high-risk groups according to age, LDH, tumor size, and SUVmax cutoff values in the validation cohort

Group	All patients, N	Probability of TET, % (n/N)	Probability of lymphoma, % (n/N)	Accuracy, % (n/N)	P value
Age				83.8 (62/74)	<0.001
Low risk	52	94.2 (49/52)	5.8 (3/52)		
High risk	22	40.9 (9/22)	59.1 (13/22)		
LDH				60.8 (45/74)	0.001
Low risk	31	96.8 (30/31)	3.2 (1/31)		
High risk	43	65.1 (28/43)	34.9 (15/43)		
Tumor size				81.1 (60/74)	<0.001
Low risk	58	87.9 (51/58)	12.1 (7/58)		
High risk	16	43.8 (7/16)	56.2 (9/16)		
SUVmax				81.1 (60/74)	<0.001
Low risk	46	97.8 (45/46)	2.2 (1/46)		
High risk	28	46.4 (13/28)	53.6 (15/28)		

LDH, lactate dehydrogenase; SUVmax, maximum standardized uptake value; TET, thymic epithelial tumor.

and anatomic information of tumors and therefore has unique advantages in tumor imaging diagnosis. It has been reported that increased ^{18}F-FDG uptake is associated with heightened risk level for TETs (20), which is in line with our research. Moreover, previous studies have reported that the ^{18}F-FDG SUVmax of lymphoma is significantly higher than that of TETs (15,16). Similarly, our study found that SUVmax (≥11.95) was an independent predictor for lymphoma, with a significantly higher OR value (30.01) than that of the other three independent factors, meaning SUVmax was the most important diagnostic factor for predicting lymphoma. The accuracy of SUVmax alone was 78.3% and 81.1% in the modeling and validation cohort, respectively. Cumulatively, the above data highlight the potential of ^{18}F-FDG PET-CT in helping the diagnosis of anterior mediastinal TETs or lymphoma. The ^{18}F-FDG SUVmax of lesions may be a key metabolic biomarker associated with the pathologic types of anterior mediastinal masses.

Treatment strategies of mediastinal lymphoma and TETs are completely disparate: surgical resection is the major treatment strategy for TETs, whereas nonsurgical chemotherapy or radiation is preferred for the treatment of lymphoma (14,21). Certain situations, such as middle-aged patients with a high LDH level, younger patients with a normal LDH level, patients with multiple enlarged lymph nodes or distant metastasis, or patients with neuroendocrine neoplasms with atypical FDG uptake, can make it difficult to distinguish the pathological type. As ^{18}F-FDG PET-CT and blood testing are routinely performed for the pretreatment workup of patients before treatment, our data have the potential to predict lymphoma in anterior mediastinal masses and may be helpful for developing suitable antitumor therapeutic strategies when clinical pathological and imaging findings failed to discriminate between lymphoma and TETs. For those with a high probability of lymphoma and an age ≤40.5 years, an LDH level ≥197 U/L, a tumor size ≥10.72 cm, and an SUVmax ≥11.95, partial resection or needle biopsy is recommended for suspected lymphoma to avoid unnecessary surgery. For those that with high probability of TETs and an age >40.5 years, an LDH level <197 U/L, a tumor size <10.72 cm, and an SUVmax <11.95, tumor resection can be considered first.

Our findings can be explained in terms of the relevant mechanisms. Lymphomas are clonal neoplasms that arise from B-cell, T-cell, and natural killer (NK)-cell subsets at various stages of maturation (22), whereas TETs are rare tumors arising from thymic epithelial cells. The difference in origin cells of lymphomas and TETs may explain the relatively young age of those with lymphoma compared to those with TETs (14) since young people tend to have more active immune cells which can increase the risk of lymphomas emergence; meanwhile, the physiological involution of the thymus progresses with age (23). LDH is a

tumor marker associated with the proliferation, metastasis, and prognosis of many cancer types (24-26). The higher serum LDH levels in lymphoma compared to those in TETs suggests that lymphoma has a more aggressive phenotype than do TETs, which may be explained by lymphoma-induced high tumor burden and activation of oncogenic factors [e.g., hypoxia-inducible factor 1α (HIF-1α) and vascular endothelial growth factor (VEGF)] (27). From the viewpoint of tumor metabolism, high ^{18}F-FDG uptake in lymphomas may be explained by the contribution of cellular energetics to the pathogenesis of lymphoma, for example the B-cell receptor (BCR)-independent diffuse large B-cell lymphoma (DLBCL)-designated oxidative phosphorylation (OxPhos) marked by increased expression of mitochondrial electron transport chain (ETC) components and BCR-dependent DLBCLs with high glycolytic flux typical of the Warburg phenotype (28). Meanwhile, the biologic mechanism of ^{18}F-FDG uptake in TETs is related to the abnormal expression of glucose transporters (Glut1) and HIF-1α (20). Our data showed that lymphoma had relatively high glucose metabolic activity compared to TETs, and thus the mechanisms underlying the metabolic differences between lymphomas and TETs merit additional research.

Lymphomas and TETs are the two most common types of anterior mediastinal masses and can be easily confused with each other; hence, in this study, we focused on distinguishing TETs from lymphomas, and those relatively easy to diagnose types (e.g., germ cell tumors with elevated serum α-fetoprotein and β-human chorionic gonadotropin levels in patients) (29) or those that rarely occur (e.g., thymolipoma, thymic cyst, parathyroid adenoma) were excluded. In selecting lymphoma types to examine, we excluded MALT lymphoma due to its low average FDG uptake value (it is not as FDG-avid as other lymphomas) as well as other rare lymphoma subtypes (e.g., anaplastic large cell lymphoma and mature T-cell and NK-cell lymphoma) (30). We believe our data for noninvasively distinguishing lymphomas from TETs may be helpful for both the diagnosis and the treatment of anterior mediastinal masses that are difficult to diagnose.

There were a few limitations in this study that should be mentioned. First, this study focused on distinguishing between only two groups of neoplasm potentially involving the anterior mediastinum. Second, we employed a retrospective study design that inevitably involved some selective bias, and a prospectively designed study will be conducted in the future to further improve the accuracy of ^{18}F-FDG PET-CT in predicting anterior mediastinal lymphoma. Third, this study was performed in a single-center and included only one hospital in the Shanghai Province of China, with most of the patients being from East China. Moreover, factors affecting the SUV of ^{18}F-FDG PET-CT (such as blood glucose level, length of uptake period, image acquisition, and reconstruction) were controlled for and standardized at a single institution. Hence, it is necessary to enroll more patients from other hospitals within and outside of Shanghai to obtain a more accurate, predictive model for mediastinal lymphoma in our subsequent study. Considering these limitations cumulatively, we intend to conduct a multicenter, prospective study to optimize the data collection for predicting anterior mediastinal lymphoma via ^{18}F-FDG PET-CT.

Conclusions

SUVmax on ^{18}F-FDG PET-CT has the potential to discriminate lymphoma from TETs for the diagnosis of anterior mediastinal masses, and the combination of clinical parameters can improve the diagnostic accuracy of SUVmax for anterior lymphoma and therefore may be helpful in preventing unnecessary operation for anterior mediastinal lymphomas.

Acknowledgments

Funding: This study was supported by the Shanghai Sailing Program (grant No. 21YF1442700), the Natural Science Foundation of Shanghai (grant No. 21ZR1458900), the National Natural Science Foundation of China (grant Nos. 82272044, 82372007, and 82202219), the Nurture Projects for Basic Research of Shanghai Chest Hospital (grant Nos. 2020YNJCM07, 2020YNJCQ11, 2020YNJCQ06, and 2021YNJCM09), and the Special Project of Integrated Traditional Chinese and Western Medicine in General Hospital of Shanghai Health Committee (grant No. ZHYY-ZXYJHZX-202023).

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-496/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.

amegroups.com/article/view/10.21037/qims-23-496/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Review Board of Shanghai Chest Hospital (No. KS1753). Individual consent for this retrospective analysis was waived.

References

1. Duwe BV, Sterman DH, Musani AI. Tumors of the mediastinum. Chest 2005;128:2893-909.
2. Almeida PT, Heller D. Anterior Mediastinal Mass. Treasure Island, FL, USA: StatPearls Publishing; 2023.
3. Savage KJ. Primary mediastinal large B-cell lymphoma. Blood 2022;140:955-70.
4. Falkson CB, Vella ET, Ellis PM, Maziak DE, Ung YC, Yu E. Surgical, Radiation, and Systemic Treatments of Patients With Thymic Epithelial Tumors: A Clinical Practice Guideline. J Thorac Oncol 2022;17:1258-75.
5. Ackman JB, Verzosa S, Kovach AE, Louissaint A Jr, Lanuti M, Wright CD, Shepard JO, Halpern EF. High rate of unnecessary thymectomy and its cause. Can computed tomography distinguish thymoma, lymphoma, thymic hyperplasia, and thymic cysts? Eur J Radiol 2015;84:524-33.
6. Zhang J, Jiang S, Li M, Xue H, Zhong X, Li S, Peng H, Liang J, Liu Z, Rao S, Chen H, Cao Z, Gong Y, Chen G, Zhang R, Zhang L. Head-to-head comparison of (18)F-FAPI and (18)F-FDG PET/CT in staging and therapeutic management of hepatocellular carcinoma. Cancer Imaging 2023;23:106.
7. Kitami A, Sano F, Ohashi S, Suzuki K, Uematsu S, Suzuki T, Kadokura M. The Usefulness of Positron-Emission Tomography Findings in the Management of Anterior Mediastinal Tumors. Ann Thorac Cardiovasc Surg 2017;23:26-30.
8. Luzzi L, Campione A, Gorla A, Vassallo G, Bianchi A, Biggi A, Terzi A. Role of fluorine-flurodeoxyglucose positron emission tomography/computed tomography in preoperative assessment of anterior mediastinal masses. Eur J Cardiothorac Surg 2009;36:475-9.
9. Zhu L, Li X, Wang J, Fu Q, Liu J, Ma W, Xu W, Chen W. Value of metabolic parameters in distinguishing primary mediastinal lymphomas from thymic epithelial tumors. Cancer Biol Med 2020;17:468-77.
10. Carter BW, Marom EM, Detterbeck FC. Approaching the patient with an anterior mediastinal mass: a guide for clinicians. J Thorac Oncol 2014;9:S102-9.
11. Marx A, Chan JKC, Chalabreysse L, Dacic S, Detterbeck F, French CA, et al. The 2021 WHO Classification of Tumors of the Thymus and Mediastinum: What Is New in Thymic Epithelial, Germ Cell, and Mesenchymal Tumors? J Thorac Oncol 2022;17:200-13.
12. Suster D, Suster S. On the Histologic Classification of Thymoma. Adv Anat Pathol 2024;31:22-33.
13. Alqaidy D. Thymoma: An Overview. Diagnostics (Basel) 2023;13:2982.
14. Jilani TN, Killeen RB, Siddiqui AH. Mediastinal Cancer. Treasure Island, FL, USA: StatPearls Publishing; 2023.
15. Yabuuchi H, Matsuo Y, Abe K, Baba S, Sunami S, Kamitani T, Yonezawa M, Yamasaki Y, Kawanami S, Nagao M, Okamoto T, Nakamura K, Yamamoto H, Sasaki M, Honda H. Anterior mediastinal solid tumours in adults: characterisation using dynamic contrast-enhanced MRI, diffusion-weighted MRI, and FDG-PET/CT. Clin Radiol 2015;70:1289-98.
16. Watanabe T, Shimomura H, Mutoh T, Saito R, Goto R, Yamada T, Notsuda H, Matsuda Y, Noda M, Sakurada A, Taki Y, Okada Y. Positron emission tomography/computed tomography as a clinical diagnostic tool for anterior mediastinal tumors. Surg Today 2019;49:143-9.
17. Sreedher G, Tadros SS, Janitz E. Pediatric mediastinal masses. Pediatr Radiol 2022;52:1935-47.
18. Jo N, Shroff GS, Wu CC, Ahuja J, Strange CD, Marom EM, Truong MT. Imaging of the mediastinum: Mimics of malignancy. Semin Diagn Pathol 2022;39:92-8.
19. Archer JM, Ahuja J, Strange CD, Shroff GS, Gladish GW, Sabloff BS, Truong MT. Multimodality imaging of mediastinal masses and mimics. Mediastinum 2023;7:27.
20. Kaira K, Endo M, Abe M, Nakagawa K, Ohde Y, Okumura T, Takahashi T, Murakami H, Tsuya A, Nakamura Y, Naito T, Hayashi I, Serizawa M, Koh Y, Hanaoka H, Tominaga

H, Oriuchi N, Kondo H, Nakajima T, Yamamoto N. Biologic Correlation of 2-[18F]-Fluoro-2-Deoxy-D-Glucose Uptake on Positron Emission Tomography in Thymic Epithelial Tumors. J Clin Oncol 2010;28:3746-53.
21. Shintani Y, Funaki S, Ose N, Kanou T, Fukui E, Kimura K, Minami M. Surgical management of thymic epithelial tumors. Surg Today 2021;51:331-9.
22. Zhuang S, Yang Z, Cui Z, Zhang Y, Che F. Epigenetic alterations and advancement of lymphoma treatment. Ann Hematol 2023. [Epub ahead of print]. Doi: 10.1007/s00277-023-05395-z.
23. Conforti F, Pala L, Giaccone G, De Pas T. Thymic epithelial tumors: From biology to treatment. Cancer Treat Rev 2020;86:102014.
24. Feng Y, Xiong Y, Qiao T, Li X, Jia L, Han Y. Lactate dehydrogenase A: A key player in carcinogenesis and potential target in cancer therapy. Cancer Med 2018;7:6124-36.
25. Jin L, Chun J, Pan C, Alesi GN, Li D, Magliocca KR, Kang Y, Chen ZG, Shin DM, Khuri FR, Fan J, Kang S. Phosphorylation-mediated activation of LDHA promotes cancer cell invasion and tumour metastasis. Oncogene 2017;36:3797-806.
26. Petrelli F, Cabiddu M, Coinu A, Borgonovo K, Ghilardi M, Lonati V, Barni S. Prognostic role of lactate dehydrogenase in solid tumors: a systematic review and meta-analysis of 76 studies. Acta Oncol 2015;54:961-70.
27. Pang Y, Lu T, Xu-Monette ZY, Young KH. Metabolic Reprogramming and Potential Therapeutic Targets in Lymphoma. Int J Mol Sci 2023;24:5493.
28. Elenitoba-Johnson KSJ, Lim MS. New Insights into Lymphoma Pathogenesis. Annu Rev Pathol 2018;13:193-217.
29. Ozgun G, Nappi L. Primary Mediastinal Germ Cell Tumors: A Thorough Literature Review. Biomedicines 2023;11:487.
30. Wang X, Wang W, Vega F, Quesada AE. Aggressive Mediastinal Lymphomas. Semin Diagn Pathol 2021. [Epub ahead of print]. doi: 10.1053/j.semdp.2021.06.010.

Cite this article as: Yan H, Wang L, Lei B, Ruan M, Chang C, Zhou M, Liu L, Xie W, Wang Y. The combination of maximum standardized uptake value and clinical parameters for improving the accuracy in distinguishing primary mediastinal lymphomas from thymic epithelial tumors. Quant Imaging Med Surg 2024;14(2):1944-1956. doi: 10.21037/qims-23-496

